REMARKS/ARGUMENTS.

1. ELECTION

Applicants confirm their previous election of Compound 5A of Example 13, which reads on a 2-oxindole sulfonamide as the caspase-3 inhibitor, and the gamma emitting halogen ^{123}I as the imaging moiety.

2. CLAIM REJECTIONS: 35 USC §101.

Claim 31 stands rejected as lacking utility.

Claim 31 has been amended to refer to a method of imaging. The objection in this regard is thus believed to have been overcome.

3. CLAIM REJECTIONS: 35 USC §112.

3.1 Claim 31.

The amendment to claim 31 is believed to overcome this objection.

3.2 Claims 1, 3, 4, 10, 14, 16-18 and 26-31.

Claims 4, 10 and 16 have now been cancelled. Hence, the objection is directed at claims 1, 3, 14, 17-18 and 16-31 only.

The objection to claim 1 is that it lacks structural elements which identify the caspase-3 inhibitor. Revised claim 1 now includes the elements of previous claim 13. The objection to claim 1 is thus believed to have been overcome.

Claims 3 and 14 depend on claim 1and thus, by definition, are also now believed to comply with 35 USC §112. Independent claims 17, 26 and 31 refer to claim 1 and hence contain all the essential features of claim 1. The objection to those claims and their associated dependent claims should therefore also be withdrawn.

4. CLAIM REJECTIONS: 35 USC §102.

4.1 Colucci.

Claims 1, 3, 4. 14, 16-18, 26-28 and 31 stand rejected as lacking novelty over Colucci (US 2006/0069038 A1).

As acknowledged by the Examiner, Colucci teaches labeling only with ^{125}I. See Claim 1 Formula I therein. The radioisotope ^{125}I is outside the scope of revised claim 1. All the remaining claims either depended on or refer to claim 1. Hence, by definition, they contain the same essential features. The present claims are therefore believed novel over Colucci and that objection should be withdrawn.

4.2 Haberkorn evidenced by Deckworth.

Claims 1, 3, 4, 14, 16-18, 26, 28, 29 and 31 stand rejected as lacking novelty over Haberkorn as evidenced by Deckwerth.

The Examiner relies on Deckworth to show that the K_i for ZVADfmk (the caspase-3 inhibitor of Haberkorn) is 820nM. Revised claim 1 stipulates that the K_i of the caspase inhibitor must be less than 500nM. In addition, the chemical structures of the caspase inhibitors are defined at (i), (ii), and (iii) of present claim 1. The ZVADfmk inhibitor of Haberkorn is outside the scope. Finally, the ^{131}I label taught by Haberkorn is also outside the scope of amended claim 1.

For all these reasons, the novelty objection to claim 1 based on Haberkorn should be withdrawn. The remaining claims all either depend on or refer to claim 1, and therefore by definition contain the same essential features. The novelty objection based on Haberkorn should therefore be withdrawn in it entirety.

4.3 Lee.

Claims 26 and 28 stand rejected as lacking novelty over Lee [J.Biol.Chem., 275(21), 16007-16014 (2000)].

Claim 26 has been amended to include the features of previous claim 29. Revised claim 26 is now believed novel over Lee, since Lee is silent on the particular derivatives defined by (a) – (c) therein. Since Lee does not teach all the essential features of claim 26, that claim is believed novel over Lee. By definition, dependent claim 28 is also novel over Lee.

5. CLAIM REJECTIONS: 35 USC §103.

5.1 Deckwerth and Haberkorn or Colucci.

Claims 1, 3, 4. 14, 16-18, 26-29 and 31 stand rejected as being obvious over the combination Deckwerth and Haberkorn or Deckwerth and Colucci.

The objection was based on the suggestion (page 13) that the combination of references teaches towards the provision of an iodine radiolabel on the oxoazepinoindoline caspase-3 inhibitors taught by Deckwerth.

Applicants point out that such inhibitors are outside the scope of present revised claim 1. Hence, amended claim 1 plus dependent and referring claims is believed non-obvious over the combination suggested by the Examiner. The objection should therefore be withdrawn in its entirety.

5.2 Lee, Haberkorn and Colucci.

Claims 1, 3, 4, 12-14, 16-18, 26-29 and 31 stand rejected as being obvious over the combination Lee, Deckwerth and Colucci.

The Examiner alleges that the person skilled in the art would be motivated to radioiodinate the 2-oxindole sulfonamide caspase-3 inhibitors of Lee because:

> "Haberkorn disclosed that ^{131}I-radiolabeled caspase-3 inhibitor IZ-VAD-fmk may be useful in imaging apoptosis".

Applicants point out that Haberkorn itself, when read in the absence of the present invention, teaches something quite different. Applicants refer to page 796-797 of Haberkorn (Discussion) where it is stated:

> "The use of a caspase inhibitor results in the trapping of one tracer molecule per activated caspase. Thus, the number of activated caspases is probably too low to induce an accumulation of the radiolabeled caspase inhibitor which is high enough to be used for imaging purposes. Instead of using an inhibitor the application of substrates for activated caspases is considered to be more successful. The coupling of charged chelates to caspase recognition sequences is expected to result in cleavage of these tracers by activated caspases and consequently in the accumulation of the metabolites. Since activated caspases are able to cleave multiple substrates this should result in an amplification of the intracellular radioactivity and, therefore, in an enhancement of the imaging signal."

Thus, Haberkorn very clearly teaches in conclusion that the caspase inhibitor approach is not suitable for imaging purposes – and that a caspase substrate should be successful. Based on Haberkorn read at the priority date of the present invention, the person skilled in the art could have no motivation to prepare further radiolabeled caspase inhibitors. Haberkorn provides a clear teaching instead towards labeled caspase substrates. Haberkorn thus teaches away from the present invention. In addition, the combination of references suggested by the Examiner is believed invalid, since it contradicts the clear teaching of Haberkorn itself against further use of the inhibitor approach.

Colucci (US 2006/0069038 A1) does not teach *in vivo* imaging using PET or SPECT as required by present amended claim 1. In addition, the teaching of Colucci is limited only to the isotope ^{125}I. That is outside the scope of revised claim 1.

Neither Lee nor Colucci teaches ^{123}I and *in vivo* imaging. Hence, no combination of those two references can provide the subject matter of present claim 1.

The obviousness rejection should therefore be withdrawn in its entirety.

5.3 Lee, Haberkorn, Colucci and Flanagan.

Claims 1, 3, 4, 10, 12-14, 16-18, 26-29 and 31 stand rejected as being obvious over the combination Lee, Deckwerth, Colucci and Flanagan.

This rejection based on the logic that, based on 5.2 above, the person skilled in the art would be motivated to combine Lee/Haberkorn/Colucci to label the caspase-3 inhibitors of Lee with ^{131}I (Haberkorn) or ^{125}I (Colucci). The additional feature of using ^{123}I instead of $^{125}I/^{131}I$ is allegedly provided in an obvious manner by Flanagan (US 5,601,801).

Applicants contend that the Examiner's logic is no longer valid. As argued at 5.2 (above), Haberkorn teaches away from the whole caspase-3 inhibitor approach. Hence, it is improper to combine the references in the manner suggested by the Examiner. The additional features of Flanagan fail to remedy the lack of motivation to label further caspase-3 inhibitors which

is the clear conclusion of Haberkorn. This obviousness objection should therefore also be withdrawn.

5.4 Lee, Haberkorn, Colucci and Hunter.

Claims 1, 3, 4, 12-14, 16-18 and 26-31 stand rejected as being obvious over the combination Lee, Deckwerth, Colucci and Hunter.

The Examiner's logic here is that the kit claim (26) is obvious over the combinations discussed above. The additional feature of claim 30 (solid phase support) is allegedly known from Hunter (US 7,018,610). Hence, the overall combination of 4 references provides the subject matter of claim 30.

As with 5.3, applicants contend that logic is no longer valid. This obviousness rejection also should therefore also be withdrawn.

6. DOUBLE PATENTING.

Claims 1, 3, 4, 10, 12-14, 16-18 and 26-31 are provisionally rejected in this regard with respect to co-pending application 11/818360.

Applicants note the objection, and will file a suitable terminal disclaimer in the event that co-pending application 11/818360 is allowed.

CONCLUSION

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application and claims are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

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